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13 March 2003
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(54) Title: ADENINE BASED INHIBITORS OF ADENYLYL CYCLASE, PHARMACEUTICAL COMPOSITIONS AND METHOD OF USE THEREOF

(57) Abstract: The present invention relates to derivatives and analogues of adenine, which inhibit adenylyl cyclase activity. The present invention also relates to a method of preventing and inhibiting a patient's fibroproliferative vasculopathy following vascular injury or a vascular surgical operation which includes administering to the patient, an effective amount of a compound according to the invention subsequent to a vascular injury, or subsequent to a vascular surgical operation, for one to two weeks after the injury or surgical operation, effective to treat or prevent a patient's fibroproliferative vasculopathy such as chronic allograft rejection or vascular restenosis following vascular trauma. The present invention also relates to a method for measuring the inhibition of adenylyl cyclase activity and a method for treating congestive heart failure.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/88 01/43294

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/52 C07D473/00 C07D473/34 C07H19/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07D C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

MEDLINE, CHEM ABS Data, BIOSIS, EPO-Internal, WPI Data, PAJ, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SHOSHANI, ILANA ET AL: "Enzymatic synthesis of unlabeled and.beta.-32P-labeled.beta.-L-2',3'-dideox yadenosine-5'-triphosphate as a potent inhibitor of adenylyl cyclases and its use as reversible binding ligand" JOURNAL OF BIOLOGICAL CHEMISTRY (1999), 274(49), 34735-34741, XP002204616 page 34735, paragraph 1 - paragraph 3 --- -/--	1,6,11, 16-19



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

4 July 2002

Date of mailing of the international search report

02 10 02

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/43294

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DESAUBRY LAURENT ET AL: "Inhibition of adenylyl cyclase by a family of newly synthesized adenine nucleoside 3'-polyphosphates." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 271, no. 24, 1996, pages 14028-14034, XP002204617 ISSN: 0021-9258 page 14028, paragraph 2; table 1 ---	1,6,11, 16-19
A	US 4 224 438 A (FAULAND ERICH ET AL) 23 September 1980 (1980-09-23) *formula II* column 8, paragraph 1; example 10 ---	1,6,11, 16-19
X	SAINTOME C ET AL: "Photochemistry of 4-Thiothymine Derivatives in the Presence of N-9-Substituted-Adenine Derivatives: Formation of N-6-Formamidopyrimidines" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY, EASTON, US, vol. 62, 1997, pages 8125-8130, XP002204618 ISSN: 0022-3263 page 8129, left-hand column, paragraph 2; example 2B ---	1
X	WEISSER M ET AL: "Adenine-Uridine Base Pairing at the Water-Solid-Interface" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 122, 2000, pages 87-95, XP002204619 ISSN: 0002-7863 page 88, left-hand column, paragraph 5; example 2 ---	1
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; HOLY, ANTONIN: "Synthesis of new mono- and disubstituted hydroxyalkyl and aminoalkyl derivatives of heterocyclic bases" retrieved from STN Database accession no. 91:20943 XP002204620 *3-(adenin-9-yl)-propionic acid* abstract & COLLECT. CZECH. CHEM. COMMUN. (1978), 43(12), 3444-65, --- -/--	1,6

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/43294

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	OKUMURA K ET AL: "SYNTHESIS AND HYPOCHOLESTEROLEMIC ACTIVITIES OF ERITADENINE DERIVATIVES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 17, no. 8, 1974, pages 846-855, XP002061464 ISSN: 0022-2623 example 64 ---	1,6
X	DATABASE CROSSFIRE BEILSTEIN [Online] BEILSTEIN INSTITUT ZUR FOERDERUNG DER WISSENSCHAFTEN, FRANKFURT AM MAIN, DE; BRN 4091148, XP002204621 abstract & ISHIDA ET AL: BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, vol. 52, 1979, page 2953 ---	1
P,X	DATABASE CROSSFIRE BEILSTEIN [Online] BEILSTEIN INSTITUT ZUR FOERDERUNG DER WISSENSCHAFTEN, FRANKFURT AM MAIN, DE; BRN 8930104, XP002204622 abstract & MAKINSKY A A ET AL: RUSSIAN JOURNAL OF BIOORGANIC CHEMISTRY, MAIK NAUKA-INTERPERIODICA, RU, vol. 27, no. 3, 2001, pages 167-172, ---	1,6
X	DATABASE CROSSFIRE BEILSTEIN [Online] BEILSTEIN INSTITUT ZUR FOERDERUNG DER WISSENSCHAFTEN, FRANKFURT AM MAIN, DE; BRN 540463, XP002204623 abstract & MASAO H ET AL: CHEMICAL LETTERS, vol. 12, 1990, pages 2251-2254, ---	1
X	DATABASE CROSSFIRE BEILSTEIN [Online] BEILSTEIN INSTITUT ZUR FOERDERUNG DER WISSENSCHAFTEN, FRANKFURT AM MAIN, DE; BRN 540463, XP002204624 abstract & BAKER AT AL: JOURNAL OF PHARMACEUTICAL SCIENCE, vol. 54, 1965, pages 1609-1615, -----	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/43294

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 11-23 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the searched group of compounds.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1,6,11,16-19

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1,6,11,16-19

compound I wherein L = Y = bond or alkylene and A = bond

2. Claims: 1-23

compound I wherein L = Y = bond or alkylene and A = carbocycle

3. Claims: 1-23

compound I wherein L = Y = bond or alkylene and A = heterocycle

4. Claims: 1-23

compound I wherein L and/or Y comprise a heteroatom and A = bond or cycle

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/43294

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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